REMARKS

1. Preliminary Remarks

a. Status of the Claims

Claims 150-177 and 179-196 are pending in this application; and claims 150-177 are withdrawn. Claims 184 and 185 are amended. Applicant respectfully requests that the amendments and remarks made herein be entered into the file history of the application. Upon entry of the amendments, claims 150-177 and 179-196 will be pending; and claims 179-196 will be under active consideration.

b. Claim Amendments

Claims 184 and 185 are amended for clarification purposes only, specifically that the limitations of these claims have antecedent basis in claim 179. Since polypeptides inherently must be encoded by polynucleotides, the scope of the claimed subject matter in claims 184 and 185 is unchanged. Applicant therefore submits that the amendments do not add new matter.

2. Patentability Remarks

a. 35 U.S.C. § 112, second paragraph

At page 3 of the Office Action, the Examiner rejects claims 184 and 185 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. The Examiner asserts that the limitation "YB-1" in claim 184 and "E2 late promoter" in claim 185 have insufficient antecedent basis. Applicant respectfully disagrees.

To provide further context, Applicant notes that previous claims 184 and 185, respectfully, refer to, "**a** YB-1 controlled promoter," and "**a** E2 later promoter." This language clearly indicated that these were the first recitations of these elements. Moreover, both elements relate to promoters that are operably linked to polynucleotides that encode polypeptides. Claim 179 recites a first and a second polypeptide that are expressed by the claimed recombinant adenovirus. Applicant submits that one of ordinary skill in the art readily understands that a polypeptide that is expressed must be encoded by a polynucleotide. Accordingly, one of skill would have ascertained that the phrase of claim 184, "wherein a YB-1-controlled promoter is operably linked to at least one polynucleotide encoding the first or second polypeptide," clearly placed a limitation on the promoter that was operably linked to the polynucleotide(s). One of skill would have applied similar reasoning to the "E2 later promoter operably linked to a polynucleotide" of claim 185.

Nevertheless, claims 184 and 185 are amended to clarify that the first and second polypeptide are respectfully encoded by a first and second polynucleotide. The amended claims now clearly indicate that the first or second polynucleotide is operably linked to a YB-1-controlled promoter (claim 184) or an E2 late promoter (claim 185). Applicant submits that amended claims 184 and 185 are not indefinite because the words and phrases contained therein are clear. *See* MPEP § 2173.05(e). In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 184 and 185 under 35 U.S.C. § 112, second paragraph.

b. 35 U.S.C. § 103

(1) Claims 179-193, 195, and 196

On pages 4-9 of the Office Action, the Examiner rejects claims 179-193, 195, and 196 under 35 U.S.C. § 103(a) as allegedly being unpatentable over by Steegenga *et al.* (Oncogene, 1998;16:349-57; "Steegenga I" hereafter) in view of Holm *et al.* (JBC, 2002;277(12):10427-34; "Holm" hereafter) and Steegenga *et al.* (Molecular and Cellular Biology, 1999;19(5):3885-94; "Steegenga II" hereafter). The Examiner asserts that Steegenga I discloses a recombinant adenovirus that expresses a first polypeptide comprising E1B and E4orf6 and a second E1A polypeptide when the adenovirus infects Hep3B cells. The Examiner further asserts that Steegenga differs from the instantly claimed subject matter by not disclosing that the E4 polypeptide is expressed before the E1B polypeptide for inactivating p53 in combination with a YB-1 polypeptide that is not E1A. The Examiner further asserts that Holm discloses the significance of YB-1 and E1B 55 Kd in adenovirus replication. The Examiner asserts that Steegenga II discloses that there is distinct regulation of p53 and p73 activity by the E1A, E1B, E4orf6, and E1A12S proteins. The Examiner contends that it would have been obvious for one of ordinary skill in the art to modify the cited reference to arrive at the claimed subject matter. Applicant respectfully disagrees.

(a) Holm is not prior art

As a preliminary matter, Applicant respectfully submits that Holm is not prior art. An obviousness rejection cannot be based on art that would not be available as prior art under 35 U.S.C. § 102. *See* MPEP § 2141.01.I ("A 35 U.S.C. 103 rejection is based on 35 U.S.C. 102(a), 102(b), 102(e), etc. depending on the type of prior art reference used and its publication or issue date"). Applicant submits that Holm is a printed publication that was published on January 11, 2002, while the earliest effective filing date of the instant application is October 15, 2002. Accordingly, Holm was published less than a year before the effective filing date of the instant application, and thus would be available as prior art only under 35 U.S.C. § 102(a).

The publication date of a publication available under 35 U.S.C. § 102(a), however, can be overcome if it is sworn behind by filing a declaration under 37 C.F.R. § 1.132. *See* MPEP § 715.01(c).I, *citing In re Katz*, 687 F.2d 450 (CCPA 1982)("An affidavit or declaration by applicant alone indicating that applicant is the sole inventor and that the others were merely working under his or her direction is sufficient to remove the publication as a reference under 35 U.S.C. 102(a)"). Submitted herewith is the declaration of the inventor, Dr. Per Sonne Holm, under 37 C.F.R. § 1.132, which was executed on January 21, 2010 (the "Holm Declaration" hereafter). In this declaration, Dr. Holm states that he is the sole inventor of the subject matter described in the instant application, "Holm" describes his own work and discloses subject matter of which he is the sole inventor, and that the other authors of Holm were merely working under his direction. In view of the Holm Declaration, Applicant respectfully submits that Holm cannot be used as a reference under 35 U.S.C. § 102(a).

(b) The claimed subject matter is not obvious over Steegenga I and II

Applicant respectfully submits that the instantly claimed subject matter is not obvious over Steegenga I and II. The basis for the Examiner's rejection is that there was some teaching, suggestion, or motivation of the prior art that would have led one of ordinary skill to combine Steegenga I with Holm and Steegenga II to arrive at the claimed invention. *See* MPEP § 2143.G. As discussed above, Holm is not prior art. Thus, under the Examiner's reasoning, the claimed invention is obvious only if (a) there was some teaching, suggestion, or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the cited references; and (b) there was reasonable expectation of success. Applicant submits that one of ordinary skill in the art had no motivation whatsoever to combine the teachings of Steegenga I and Steegenga II to arrive at the claimed subject matter.

The instantly claimed subject matter relates to a recombinant adenovirus that, upon infecting a eukaryotic cell, expresses an E1B and/or an E4 polypeptide **prior** to expressing an E1A polypeptide. This order of expression is **reverse** that of a wild-type adenovirus. Despite this reversal, the claimed adenovirus replicates efficiently, and is capable of lysing infected cells. *See* Instant Application at page 15, second paragraph. Additionally, the claimed adenovirus can replicate only in tumor cells where YB-1 is overexpressed or derergulated, and . *See Id.* at page 74, paragraph 2.

In stark contrast, Steegenga I and Steegenga II **are completely silent** as to the order of expression of E1A, E1B, and E4. They disclose absolutely nothing about how the order of

expressing these proteins affects adenovirus replication. The Examiner refers to Figure 6 of Steegenga I as allegedly disclosing a recombinant adenovirus that when it infects Hep3B cells, expresses first polypeptide comprising E1B and E4orf 6, and a second E1A polypeptide. Office Action at page 5, paragraph 2. Applicant respectfully submits that the Examiner has mischaracterized the import of Figure 6. Figure 6 has nothing to do with a recombinant adenovirus. Figure 6 clearly deals only with **transient** transfection of p53-negative Hep3B cells with plasmids encoding E1B or E4orf6. The materials and methods make this even clearer. *See* Steegenga I at page 356, column 2, third paragraph. Furthermore, Figure 6 discloses nothing about E1A.

Not only does Figure 6 fail to disclose any kind of virus whatsoever, but nowhere in the remainder of Steegenga I is a single recombinant adenovirus with an altered order of gene expression disclosed. The section "Adenoviruses and virus techniques," makes clear that the only adenoviruses disclosed in Steegenga I have some sort of deletion: in the large E1B gene (*dl*1520, ONYX-0.015, R443, and H326), in the orf6 gene (*dl*355), or of the entire E1 region (CMVLacZ). Steegenga I at page 355, column 2, paragraph 3. Thus, Steegenga I fails to teach or suggest all the instant claim limitations.

The failings of Steegenga II are even more stark. Steegenga II discloses nothing but a series of transient transfection experiments using plasmids encoding various adenovirus proteins, sometimes in combination with wild-type adenovirus infection. In fact, the only adenovirus disclosed in this reference is a wild-type adenovirus. *See* Steegenga II, page 3886, column 1, paragraph 4. Not a single recombinant adenovirus is disclosed, let alone one in which the order of protein expression is changed. Thus, Steegenga I and Steegenga II combined fail to teach or suggest all of the instant claim limitations.

Moreover, based on the disclosure of Steegenga I and Steegenga II, it is **impossible** for one of ordinary skill in the art to know how the order of E1A, E1B, and E4 expression affects adenovirus replication, or for that matter, why the order of expression of these proteins is even relevant to adenovirus replication. Whether E1B and E4orf6 are capable of reducing p53 expression after infection is irrelevant. Further, as the Examiner admits, Steegenga I discloses that expression of E1A is not even required for the effects of adenovirus infection on p53. Office Action at page 5, paragraph 2. Accordingly, the Examiner has failed to articulate a reason why one of skill would have been motivated to alter the order of E1B, E4, and E1A expression in a recombinant adenovirus to arrive at the instantly claimed subject matter.

In the absence of the prior art teaching or suggesting all of the claim limitations, the Examiner, "must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art." MPEP § 2141.III. Applicant respectfully submits that the Examiner has not set forth a rationale to explain why it would be obvious to arrive at a recombinant adenovirus that expresses E1B and/or E4 **before** E1A when it infects a eukaryotic cell, from references that teach nothing but wild-type or deletion-mutant strains of adenovirus, and that disclose absolutely nothing about the significance of expression order to efficient adenovirus replication. The adenovirus deletion strains of Steegenga I **do not change the order of protein expression**, they affect only whether certain genes are expressed at all, or the structure of the protein expressed. Applicant submits that there would have been no reason for one of skill to modify the order of protein expression in an adenovirus based on the disclosures of Steegenga I and Steegenga II. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 179-193, 195, and 196 under 35 U.S.C. § 103(a).

(2) Claim 194

On pages 8 and 9 of the Office Action, the Examiner rejects claim 194 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Steegenga I in view of Holm, Steegenga II, and further in view of Li *et al.* (Cancer Research, 2001;61:6428-36; "Li" hereafter). The Examiner refers to the arguments as applied to claims 179-193, 195, and 196, and asserts further that the while Steegenga I, Steegenga II, and Holm do not teach an IRES sequences separating a nucleic acid that encodes E1B and/or E4, and a nucleic acid that encodes E1A, Li provides sufficient disclosure to obviate the instantly claimed subject matter. Applicant respectfully disagrees for the reasons set forth above. Li does nothing to overcome the fatal deficiencies of Steegenga I and Steegenga II. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claim 194 under 35 U.S.C. § 103(a).

c. Obviousness Type Double Patenting

On pages 9-11 of the Office Action, the Examiner provisionally rejects claims 179-196 on grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims in copending U.S. Patent Application Nos. 10/579,543, filed May 14, 2006 (the "'543 Application" hereafter)(claims 104-117) and 10/451,210, filed November 17, 2003 (the "'210 Application" hereafter)(claims 47-51, 53, 59, 60, and 65). Applicant respectfully requests that the Examiner hold the rejection over the '210 Application in abeyance until there is allowable subject

matter, at which time the Applicant will consider amending the claims in the '210 Application, or filing a terminal disclaimer. Additionally, the instant application was filed on April 14, 2005, and thus before the '543 Application. Because the instant application was filed earlier, Applicant respectfully requests that the obviousness-type double patenting rejection over the '543 Application be withdrawn pursuant to MPEP § 804.I.B1.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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